UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

IN RE: Acetaminophen – ASD-ADHD Products Liability Litigation This Document Relates To: *All Cases*	Docket No.: 22-md-3043 (DLC)

DEFENDANTS' REPLY IN SUPPORT OF MOTION TO EXCLUDE PLAINTIFFS' GENERAL CAUSATION EXPERTS' OPINIONS REGARDING AUTISM SPECTRUM DISORDER

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Plaintiffs do not dispute that virtually every regulatory, scientific and medical body to address the proposed relationship between in utero exposure to acetaminophen and ASD has concluded that the relevant evidence is "unable to support a determination of causality."[1] Nor can they refute that the Second Circuit recently affirmed the exclusion of expert testimony advancing a similar theory with respect to a prescription antidepressant. *See Daniels-Feasel v. Forest Pharms., Inc.*, No. 22-146, 2023 U.S. App. LEXIS 19448 (2d Cir. July 28, 2023), *aff'g* No. 17-4188, 2021 WL 4037820 (S.D.N.Y. Sept. 3, 2021). Instead, plaintiffs argue that because they have found a cadre of credentialed experts who are willing to buck the scientific consensus and who purport to base their conclusions on "scientifically acceptable" weight-of-evidence and Bradford Hill methodologies, the Court should allow them to present their unreliable opinions to juries. Plaintiffs' superficial approach to expert evidence, if accepted, would eviscerate the Court's gatekeeping function and abrogate the fundamental reliability requirements of *Daubert* and Rule 702. Under Rule 702, plaintiffs must demonstrate—by a preponderance of the evidence—not only that their experts have invoked reliable methods by name, but also that they reliably ***applied*** those methods in reaching their conclusions. Plaintiffs' oppositions underscore their failure to satisfy this standard.

Plaintiffs try to prop up the limited, conflicting and unsupportive epidemiologic data underlying their experts' ASD opinions with literature on ADHD, hypothesis-generating "proxy" studies, and results-oriented approaches to animal studies and Bradford Hill that are virtually indistinguishable from those recently rejected in *Daniels-Feasel*. None of this unscientific scaffolding can compensate for the lack of science supporting their positions.

First, plaintiffs fail to establish the reliability of their experts' approach to the two very

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[1] ECF 1105, at 2 ("FDA Letter") (citation omitted).

limited studies with ASD-diagnosis endpoints (Ji 2020 and Liew 2016) that reported a statistically significant association between acetaminophen and ASD. Plaintiffs essentially concede that neither Dr. Louie nor Dr. Hollander accounted for the significant limitations of Ji 2020 (e.g., the fact that it measured acetaminophen at or just prior to birth) or Liew 2016 (e.g., the authors' explicit warning that confounding by genetics or by indication is a potential alternative explanation for the reported association), much less reconciled those studies with the majority of data finding no statistically significant association. Although plaintiffs insist that Drs. Baccarelli and Cabrera ***acknowledged*** these issues in their reports, Rule 702 required them to meaningfully ***reconcile*** their conclusions with these limitations and contrary evidence. They failed to do so, and nothing in plaintiffs' opposition briefing shows otherwise.

Nor can plaintiffs' experts fill the gap left by studies on acetaminophen and ASD by relying on studies evaluating a potential association between prenatal acetaminophen exposure and various developmental and behavioral screening measures. These studies are too imprecise, subjective and over-inclusive to support a reliable general causation opinion. Plaintiffs trumpet various studies cited by Dr. Hollander that supposedly "validate" the use of screening tests, but those sources instead show the opposite: that screening measures are not a reliable substitute for ASD diagnoses. Dr. Hollander's "transdiagnostic" approach is even more unreliable insofar as he seeks to transform a simple observation that ASD and ADHD can have overlapping features into a blank check to treat studies of these conditions (indeed, virtually all neurodevelopmental disorders) interchangeably. This approach contravenes the longstanding proscription against relying on supposed evidence that a medication causes one condition as reliable scientific proof that it causes another.

Second, plaintiffs' various arguments regarding their experts' Bradford Hill analyses all

perpetuate their unreliable conflation of ASD and ADHD, repeatedly addressing (just like their experts) each of the Bradford Hill criteria in a manner that lumps all of the literature on the two proposed causal theories together in an effort to obscure the paucity of studies finding any association with ASD. Plaintiffs' approach to each of the Bradford Hill requirements is similarly unscientific and superficial. They assert that associations are strong even when Dr. Cabrera considers them "moderate" or "low"; they fail to justify their experts' anti-scientific disregard of statistical significance; they cannot point to any reliable support for their experts' dose-response opinions; and they mischaracterize defendants' arguments on temporality and coherence.

Third, plaintiffs downplay *Daniels-Feasel*, arguing that Drs. Cabrera and Pearson were right to rely on animal studies in attempting to plug the fundamental gaps in the epidemiologic literature and that *Daniels-Feasel*'s holding turned on the presence of contradictory epidemiological evidence. This argument fails both because the epidemiological evidence of an association was more robust in *Daniels-Feasel* than here, and because the court's reasoning as to animal studies hinged on a proposition that is equally applicable here: i.e., animal behaviors are not a reliable proxy for the uniquely human behaviors that characterize ASD.

Finally, plaintiffs also fail to refute defendants' arguments that Dr. Baccarelli did not reliably apply the Navigation Guide methodology; that his opinions reflect a 180-degree reversal from his prior published writing (a telltale sign of a made-for-litigation approach to causation); and that Dr. Louie's 28-day theory is just his own *ipse dixit*.

ARGUMENT

Plaintiffs repeatedly contend that their experts' opinions on ASD are admissible because the experts purported to employ weight-of-evidence, Bradford Hill and Navigation Guide methodologies that courts have regarded as "scientifically acceptable." (Cabrera Opp'n at 13 (quoting *Daniels-Feasel*, 2021 WL 4037820, at *6); *see also* Baccarelli Opp'n at 1 ("Baccarelli

deployed both the standard Bradford Hill methodology . . . plus the Navigation Guide . . . .").)

But "[p]laintiffs' mere assertion that their experts followed [such] methodologies is insufficient to carry their burden that their experts' opinion is reliable." *In re Zantac (Ranitidine) Prods. Liab. Litig.*, 644 F. Supp. 3d 1075, 1278 n.164 (S.D. Fla. 2022); *see also McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1244 (11th Cir. 2005) ("The expert's assurances that he has utilized generally accepted scientific methodology [are] insufficient.") (citation omitted). Rather, plaintiffs must demonstrate that their experts reliably applied those methods—i.e., that they "thoroughly analyze[d] the strengths and weaknesses of any inconsistent research and sufficiently reconcile[d] [their] opinion[s] with contrary authority." *Daniels-Feasel*, 2021 WL 4037820, at *15. For this reason, where an expert conducts a "flawed and misleading Bradford Hill analysis," merely incanting the term "Bradford Hill" does not carry the day. *Id.* at *16.

Plaintiffs attempt to distinguish *Daniels-Feasel*, but it is on all fours with this litigation. As that court noted, "no regulatory agency, professional organization, peer-review study, or medical treatise concludes that Lexapro causes ASD, and the FDA has approved its prescription to pregnant women." *Id.* at *7. And even though the epidemiologic data there were, if anything, more robust than the data here, including three different observational studies that reported statistically significant relative risks of 3.34, 2.2 and 1.45, the court explained that two of the studies were subject to "limitations that make it 'difficult to conclusively dismiss the possibility that the observed associations are wholly attributable to confounding [by indication],'" limitations the expert improperly dismissed. *Id.* at *10 (citation omitted). Moreover, the expert "disregard[ed]" studies that "failed to report a statistically significant association" based on supposed weaknesses that also applied to the studies touted by the expert in support of his opinions. *Id.* at *8-9.

Plaintiffs argue both that the epidemiologic evidence is stronger in this case and that their experts did not actually "ignore[] and disregard[] conflicting lines of evidence." (Baccarelli Opp'n at 44; *see also* Cabrera Opp'n at 24.) But the relevant epidemiologic evidence here is weaker than in *Daniels-Feasel*, in part because unlike Lexapro, acetaminophen is an over-the-counter medication indicated for a variety of conditions, and is taken without medical records evidencing timing, dose or duration of exposure. As a result, the two on-point studies underlying plaintiffs' experts' opinions in this litigation are marred by even more fundamental "limitations," all of which plaintiffs' experts either ignore or brush aside without any scientific basis. Further, plaintiffs' experts do not reconcile the findings of these limited studies with the remainder of the literature finding no statistically significant association between prenatal acetaminophen exposure and an ASD diagnosis. And plaintiffs' experts compound these fundamental methodological defects by conflating ASD and ADHD in a transparent effort to inflate the body of relevant evidence. In short, this is not some disagreement over the "interpretation of the studies" (Baccarelli Opp'n at 1; *see also, e.g.*, Cabrera Opp'n at 3; Hollander Opp'n at 2); rather, plaintiffs' experts' opinions reflect a "selective and biased" approach to causation, which is "demonstrative of an unreliable application of purportedly sound scientific methodology." *Daniels-Feasel*, 2021 WL 4037820, at *12.[2] This alone requires exclusion of all their ASD causation opinions.

[2] Plaintiffs' cases do not support a different result. For example, in *Amorgianos v. National Railroad Passenger Corp.*, 303 F.3d 256 (2d Cir. 2002) (cited in Baccarelli Opp'n at 1), the Second Circuit "reject[ed] [the] plaintiffs' assertion that the district court's method of evaluating the reliability of the experts constituted a usurpation of the jury's and experts' roles." *Id.* at 269. As the Second Circuit explained, the district court properly "conducted an extremely thorough review of the scientific literature on which [the] plaintiffs' experts relied" and concluded that there was an insufficient "fit between the experts' opinion and the scientific literature on which they relied." *Id.*

I. PLAINTIFFS' EXPERTS DO NOT RELIABLY IDENTIFY A "CLEAR-CUT" ASSOCIATION IN THE OVERALL BODY OF ASD LITERATURE.

As explained in defendants' opening brief, the body of epidemiologic literature assessing the proposed association between in utero acetaminophen exposure and an ASD diagnosis—which includes two studies that found no statistically significant association (Ji 2018 and Saunders 2019), a similar finding in febrile women (Hornig 2018) and two other studies that are inconsistent with each other and rife with limitations (Ji 2020 and Liew 2016)—is too limited and weak to support an "association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance."[3] In response, plaintiffs attempt to analogize the limited data underlying their experts' ASD opinions to the data surrounding valproic acid and asbestos.[4] Plaintiffs also attempt to rehabilitate their experts' unscientific approach to the available data. Both efforts fail.

A. Plaintiffs Disregard The Scientific Record.

Plaintiffs devote significant portions of their oppositions to reimagining the scientific record and urging the Court to credit their experts' opinions based on logic or rationales that the witnesses themselves did not supply.[5] "None of these elaborations by counsel is relevant. The subject of this motion is the proposed testimony of experts, not the theories of the lawyers." *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 407 (S.D.N.Y. 2005) (excluding general causation opinions, reasoning that "plaintiffs' counsel at every stage have gone further than their

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[3] Hill, *The Environment and Disease: Association or Causation?* 295, 295 (1965) (Mot. Ex. 81).

[4] In their opposition to plaintiffs' motion to exclude the opinions of Dr. Jennifer Pinto-Martin, defendants erroneously cited an outdated version of the valproic acid label, which (unlike the 2020 label) did not speak in terms of a "causal association." (ECF 1241, at 2, 34.) That mistake does not change the fact that this litigation is about whether acetaminophen causes ASD and ADHD, not whether valproic acid causes either disorder. As further detailed below, the valproic acid label does not support plaintiffs' experts' opinions here for multiple reasons.

[5] Plaintiffs' counsel presaged this lawyer-driven approach when they informed the Judicial Panel on Multidistrict Litigation that the "causation" theory is "currently being built by a bunch of lawyers working on the case." *See* Sept. 29, 2022 JPML Hr'g Tr. 17:2-3 (Ex. 1).

experts"); *see also Tamraz v. Lincoln Elec. Co.*, 620 F.3d 665, 672-73 (6th Cir. 2010) (the expert's "opinion cannot escape its own logic"). But even if counsel argument could fill the gaps in an expert's opinions, plaintiffs' efforts would still fail.

First, plaintiffs argue that their counsel-created forest plots (i.e., a graphical display of study results) are "worth a thousand words" and demonstrate that their experts reliably concluded that there is an association between prenatal acetaminophen exposure and ASD. (Baccarelli Opp'n at 34.) But those plots are highly misleading—and echo the cherry-picking methods of plaintiffs' experts—because they represent only ***some*** of the ***many*** risk ratios in each study, and many of the omitted risk ratios are below the null or are statistically insignificant. For example, the plot corresponding to Liew 2016 selectively omits any point estimates below 1.0, such as for infantile autism without Hyperkinetic Disorder ("HKD") (aHR=0.98, 95% CI 0.77-1.26). Plaintiffs' graph also fails to account for the fact that Saunders 2019 did not report a point estimate because it did not find a statistically significant association. And plaintiffs omit that the most recent attempt to pool the available epidemiologic literature (Ricci 2023) found that there was an "insufficient number of comparable studies" to complete a meta-analysis with respect to acetaminophen and ASD.[6]

Second, plaintiffs falsely contend that JJCI's own scientists and experts have already deemed plaintiffs' experts' conclusions to be "reasonable" and not "junk science." (Baccarelli Opp'n at 1 (citations omitted); *see also id.* at 4, 19.) Contrary to their representations, [redacted]

[redacted]

[redacted]

[6] Ricci, *In Utero Acetaminophen Exposure and Child Neurodevelopmental Outcomes: Systematic Review and Meta-Analysis*, 37 Paediatr. Perinat. Epidemiol. 473, 482 (2023) ("Ricci 2023") (Mot. Ex. 121).

[redacted] The fact that JJCI took all of the literature seriously and "raised questions" about proposed theories is laudable and "cannot serve as admissions of general causation." *See In re Mirena IUD Prods. Liab. Litig.*, 202 F. Supp. 3d 304, 324-25 (S.D.N.Y. 2016) ("These emails 'demonstrate that [Bayer] employees raised questions' about the timing of perforations in Mirena users . . . . They do not amount to admissions that secondary perforation exists.") (citation omitted). Further, although plaintiffs claim that Dr. Jennifer Pinto-Martin testified to an "ongoing debate" about a proposed causal relationship (Baccarelli Opp'n at 1-2 (citation omitted)), she also made clear that only one side of that debate has scientific support (Dep. of Jennifer Pinto-Martin ("Pinto-Martin Dep.") 562:2-9 (Opp'n Ex. 25) ("I don't think a reasonable epidemiologist could disagree with my conclusion based on this body of evidence that there is no credible support for a causal association . . . .")).

Third, plaintiffs contend that the Second Circuit countenanced a theory of general causation based on "[f]ar [l]ess [e]vidence" in *In re Joint Eastern & Southern District Asbestos Litigation*, 52 F.3d 1124 (2d Cir. 1995). (Baccarelli Opp'n at 21.) But the court there found sufficient evidence of causation as to asbestos—i.e., "a carcinogen"—noting that there were "12 different epidemiological studies," seven of which found statistically significant associations with gastrointestinal cancers. 52 F.3d at 1129, 1135 n.19 (citation omitted). The court also noted that two different government regulatory agencies "concluded, upon their review of [those] studies, that a ***strong*** causal link does exist between asbestos exposure and gastrointestinal

cancer, including colon cancer." *Id.* at 1135 (emphasis added).[7] Here, by contrast, as defendants have explained at length, there are only five relevant epidemiological studies (the majority of which found no statistically significant association), which is one reason why the FDA has repeatedly concluded that the available data do not support a causal link. Although plaintiffs point to a smattering of statements from the FDA purportedly "demonstrat[ing] that reasonable epidemiologists can opine" that causation has been shown (Baccarelli Opp'n at 24), those statements reflect, at most, that studies "raise the possibility of neurodevelopmental harm" (*id.* (quoting ECF 483-1 at FDACDER000014))—which "falls far short of what is necessary for plaintiffs to sustain their burden on this element"—i.e., that ASD "causation is more likely than not." *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 387 F. Supp. 3d 323, 351 (S.D.N.Y. 2019) (citation omitted), *aff'd*, 982 F.3d 113 (2d Cir. 2020). No amount of parsing can change the FDA's recent unequivocal conclusion that the data are "unable to support a determination of causality."[8]

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[7] Plaintiffs' reliance on *In re Joint Eastern* is all the more misplaced because "[t]he central question before [the Second Circuit] [was] the standard governing federal judges' evaluations of the sufficiency—as opposed to admissibility—of scientific evidence already admitted." 52 F.3d at 1126. As the Second Circuit explained, although *Daubert* "expand[ed] district courts'" gatekeeping responsibility in assessing the reliability of expert evidence, the Supreme Court "left the traditional sufficiency standard intact." *Id.* at 1132.

[8] FDA Letter at 1-2 (citation omitted). Plaintiffs also suggest that the FDA's repeated judgment does not bear on the reliability of their experts' opinions, noting that the U.S. Attorney for the Southern District of New York recently stated that it is the function of this Court, not the FDA, "to review the admissibility of expert and other evidence in these matters." (*See* Baccarelli Opp'n at 23 (citation omitted).) But the fact that the question of admissibility lies with the Court (not the FDA) does not mean the agency's expert regulatory judgment is irrelevant to that question, as both *Daniels-Feasel* and plaintiffs' own authority make clear. *See Daniels-Feasel*, 2021 WL 4037820, at *7 (excluding expert in part because "no regulatory agency . . . concludes that Lexapro causes ASD, and the FDA has approved its prescription to pregnant women"); *see also In re Joint E.*, 52 F.3d at 1135-36 (reversing a district court's ruling that had failed to "mention . . . federal government agency reports," all of which "bolstered" the plaintiff's theory of general causation). *In re Bair Hugger Forced Air Warming Devices Products Liability Litigation*, 9 F.4th 768, 789 (8th Cir. 2021), *cert. denied*, 142 S. Ct. 2731 (2022) (cited in Baccarelli Opp'n at 23), does not hold otherwise. In that case, the Eighth Circuit noted in a single, conclusory sentence that one letter from the FDA reporting the agency's conclusion that it was "'unable to identify a consistently reported association' between forced-air warming and surgical-site infection" did not warrant exclusion of the plaintiffs' general causation evidence. *Id.* at 789 (citation omitted). The Eighth Circuit did not suggest that FDA judgments on proposed causal theories are irrelevant to the *Daubert* inquiry.

Plaintiffs similarly attempt to liken the scientific record here to that concerning valproic acid (an anti-seizure prescription medication), noting that just two studies are cited in support of that drug's label's "state[ment] that 'the weight of the evidence supports a causal association' between in-utero exposure of [valproic acid], ASD, and ADHD." (Baccarelli Opp'n at 20 (quoting Am. Rep. of Andrea Baccarelli ("Baccarelli Rep.") at 53, 167 (Mot. Ex. 2)).) However, the respective bodies of literature are not remotely comparable, as reflected by the ASD study described on the valproic acid label itself, which actually adjusted for potential confounding factors (including psychiatric history) and was supported by robust prescription-based data on dosages and durations of use.[9] Here, by contrast, the evidence regarding acetaminophen (an over-the-counter medication) is not supported by similar information on exposure and suffers from weak relative risks, inconsistent study findings and numerous other limitations, leading the FDA to repeatedly make clear that the data are "unable to support a determination of causality."[10] In any event, "[i]t is widely recognized that" the FDA—which "err[s] on the side of caution"—relies on a "lesser showing of harm to the public than the preponderance-of-the-evidence . . . used to assess tort liability." *In re Mirena*, 387 F. Supp. 3d at 356 (citation omitted). In short, the valproic acid analogy only serves to highlight the unreliable nature of plaintiffs' experts' opinions here.[11]

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[9] *See* Christensen, *Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism*, 309(16) JAMA 1696 (2013) (Opp'n Ex. 58).

[10] FDA Letter, at 2.

[11] Indeed, the fact that plaintiffs refer to valproic acid six times on the very first page of their Pinto-Martin reply brief (as compared to their singular reference to acetaminophen on the same page) (*see* ECF 1310, at 1) suggests that plaintiffs wish to deflect the Court's attention from the relevant body of literature (which, as explained above, does not provide the same support for causation as studies of valproic acid) and ultimately underscores the degree of overreach underlying their experts' opinions.

B. Drs. Baccarelli, Cabrera, Hollander And Louie Cherry-Pick, Misread And Twist Study Results.

1. Drs. Baccarelli, Cabrera, Hollander And Louie Do Not Account For Significant Limitations In The Studies On Which They Rely.

As explained in defendants' opening brief, plaintiffs' experts rely on two highly limited studies (Ji 2020 and Liew 2016) in concluding that an association exists between prenatal acetaminophen exposure and a diagnosis of ASD. (*See* Mot. at 27-32.) In response, plaintiffs do not appear to dispute that neither Dr. Louie nor Dr. Hollander made any effort to address these limitations, even though both experts gave significant "weight" to the two studies. (*See, e.g.*, Am. Rep. of Stan Louie ("Louie Rep.") ¶ 83 (Mot. Ex. 9) ("I assigned greater weight to studies that . . . used biomarkers," such as Ji 2020); *id.* ¶ 78 (relying on Liew 2016); Rebuttal Rep. of Eric Hollander ("Hollander Rebuttal Rep.") at 11 (Mot. Ex. 12) (similar with respect to Ji 2020); Hollander Rebuttal Rep. at 13 (similar for Liew 2016).)

Plaintiffs claim that Drs. Baccarelli and Cabrera "described, analyzed, and exhaustively 'accounted for' the limitations" in Ji 2020 and Liew 2016. (Baccarelli Opp'n at 36; *see also* Cabrera Opp'n at 19.) But the citations they provide show that Drs. Baccarelli and Cabrera, at most, identified the "limitations" (Baccarelli Opp'n at 36; Cabrera Opp'n at 19), not that they "thoroughly analyze[d] the . . . weaknesses" of those studies or "sufficiently reconcile[d]" them with their ultimate conclusions. *See Daniels-Feasel*, 2021 WL 4037820, at *15; *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 604-05 (D.N.J. 2002) (while expert acknowledged that some studies on which he relied "had limitations," he failed to grapple with them or pay them proper attention in reconciling them with his ultimate conclusions), *aff'd*, 68 F. App'x 356 (3d Cir. 2003).

Ji 2020. Plaintiffs fail to address that Dr. Cabrera ignored perhaps the most fundamental weakness of Ji 2020: because it measured acetaminophen in maternal and umbilical cord blood

samples at the time of birth, it "may at most reflect maternal use of acetaminophen during the peripartum period."[12] This is a remarkable omission because Dr. Cabrera testified at his deposition that the proper question is whether acetaminophen exposure occurred before the "critical" window for brain development, which he believes is the second trimester. (Dep. of Robert Cabrera ("Cabrera Dep.") 23:13-24:2, 230:9-12 (Mot. Ex. 7).)[13]

Plaintiffs do point to Dr. Baccarelli's statements in his report that "[l]imitations . . . include the ability to measure acetaminophen levels in the umbilical cord at only one point in time [at the time of birth]." (Baccarelli Opp'n at 36 (quoting Baccarelli Rep. at 90).) But Dr. Baccarelli simply mentions this limitation and moves on, without explaining why it did not affect his opinions. Dr. Baccarelli's silence on this issue is particularly troubling in light of plaintiffs' claim that Dr. Baccarelli disregarded Ji 2018 (which used the same cohort and found no statistically significant association between acetaminophen in the mother's blood one to three days after delivery and the development of ASD) because of its purportedly "highly imperfect proxy for in utero APAP exposure" (Baccarelli Opp'n at 39), a characterization that similarly applies to Ji 2020. *See Daniels-Feasel*, 2021 WL 4037820, at *9 (excluding expert who disregarded "express limitations" of cited studies, while at the same time "disregarding those studies that do not support his conclusions because they suffer from the same limitations").

Plaintiffs also quote Dr. Baccarelli's and Dr. Cabrera's acknowledgments that "the

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[12] Ji, *Association of Cord Plasma Biomarkers of In Utero Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder & Autism Spectrum Disorder in Childhood*, 77(2) JAMA Psychiatry 180, 188 (2020) ("Ji 2020") (Mot. Ex. 89).

[13] Plaintiffs also do not claim that their experts meaningfully addressed the bizarre finding that all the umbilical cord samples in the study contained acetaminophen. Although plaintiffs highlight Dr. Baccarelli's recognition of this limitation in his report (*see* Baccarelli Opp'n at 36 (citing Baccarelli Rep. at 90)), they do not explain how Dr. Baccarelli accounted for it in reaching his opinions.

study . . . was unable to exclude the potential residual confounders of genetic and environmental factors." (Cabrera Opp'n at 19 (quoting Am. Rep. of Robert Cabrera ("Cabrera Rep.") at 132 (Mot. Ex. 6)); *see also* Baccarelli Opp'n at 36 ("Limitations of this study include . . . the theoretical possibility of residual confounding.") (quoting Baccarelli Rep. at 90).) But again, plaintiffs fail to cite anything from either expert indicating that the expert ***accounted*** for genetic confounding (as opposed to just ***identifying*** it without any explanation). That omission is particularly glaring because, when the authors of Ji 2020 adjusted for maternal mental health, the only previously reported statistically significant association (i.e., the association between acetaminophen in umbilical cord blood and ASD for the third tertile) became attenuated to a non-statistically-significant level, raising serious questions about whether the reported association was being driven by genetic factors.[14]

Plaintiffs contend that Drs. Baccarelli and Cabrera sufficiently accounted for the potential for genetic confounding by relying on "the results from *other* studies in the literature showing no link between autism-related genes and APAP use." (Baccarelli Opp'n at 38 (citing Baccarelli Rep. at 123; Rebuttal Rep. of Andrea Baccarelli ("Baccarelli Rebuttal Rep.") at 3 (Mot. Ex. 16)); *id.* at 11-12; *see also* Cabrera Opp'n at 17 ("concur[ring] with Dr. Baccarelli's 'analysis and conclusions'") (citation omitted).) But the studies they cite in support of this claim primarily pertain to ADHD and neurodevelopmental symptoms, not ASD diagnosis.[15]

The only study plaintiffs cite that purported to address the role of genetics in ASD

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[14] Ji 2020 at Supplementary eTable 3. The fact that Ji 2020—like Ji 2018—reported no statistically significant association for any metric assessing acetaminophen and ASD according to maternal blood plasma—is yet another red flag that neither plaintiffs nor their experts meaningfully address.

[15] *See, e.g.*, Baccarelli Opp'n at 11 (citing Bornehag 2017—language development in offspring at 30 months of age); Baccarelli Rep. at 123 (addressing Stergiakouli 2016—neurodevelopmental symptoms); Baccarelli Rebuttal Rep. at 3 (discussing Trønnes 2020—the activity level; Ystrom 2017—ADHD); Cabrera Rep. at 143-45 (addressing Liew 2019—ADHD; Thompson 2014—symptoms of ADHD).

etiology is Leppert 2019. Although that study found that maternal polygenic risk scores associated with a child's ASD were not associated with acetaminophen use during pregnancy, the authors expressly cautioned that such scores "explain only a small amount of variance in heritability of neurodevelopmental disorders ['NDDs']"[16]—i.e., "a polygenic risk score does not capture the entire universe of genetic risk." (Pinto-Martin Dep. 158:9-14.) By contrast, as even Dr. Louie recognizes, sibling-control analyses are far more instructive (*see* Dep. of Stan Louie 114:19-115:13 (Mot. Ex. 10)), which is why plaintiffs' and their experts' failure to address numerous sibling-control analyses debunking prior theories that various exposures and events (e.g., prenatal antidepressant exposure, labor-inducing medication and c-sections) were linked to ASD is a fatal flaw in their methods.[17]

Plaintiffs also attempt to defend Dr. Cabrera's approach to genetic confounding on the ground that NDDs "such as ASD and ADHD result from an interaction *between* genes and environmental factors." (Cabrera Opp'n at 14 (citing Rebuttal Rep. of Robert Cabrera at 2-6 (Opp'n Ex. 8)).) But defendants and their experts have not disputed that environmental factors,

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[16] *See* Leppert, *Association of Maternal Neurodevelopmental Risk Alleles With Early-Life Exposures*, 76(8) JAMA Psychiatry 834, 840 (2019) ("Leppert 2019") (Mot. Ex. 97).

[17] *See, e.g.*, Vega, *Implementation of Advanced Methods for Reproductive Pharmacovigilance in Autism: A Meta-Analysis of the Effects of Prenatal Antidepressant Exposure*, 177(6) Am. J. Psychiatry 506 (2020) (Mot. Ex. 156); Oberg, *Association of Labor Induction With Offspring Risk of Autism Spectrum Disorders*, 170(9) JAMA Pediatrics 1 (2016) (Mot. Ex. 113); Curran, *Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study*, 72(9) JAMA Psychiatry 935 (2015) (Mot. Ex. 62). Plaintiffs also claim that Alemany 2021—a meta-analysis that reported a statistically significant association between acetaminophen and "ASD symptoms" of 1.19 (95% CI 1.07-1.33)—found that it is "unlikely that the observed relationship between prenatal acetaminophen and [ASD symptoms] and ADHD symptoms is entirely explained by unmeasured confounding." (Baccarelli Opp'n at 11 (quoting Alemany, *Prenatal and Postnatal Exposure to Acetaminophen in Relation to Autism Spectrum and Attention-Deficit and Hyperactivity Symptoms in Childhood: Meta-Analysis in Six European Population-Based Cohorts*, 36 Euro. J. Epidemiol. 993, 1001 (2021) ("Alemany 2021") (Mot. Ex. 28)).) That statement was made in the context of the authors noting that "although results were adjusted by several lifestyle and health factors that have been shown to be associated with prenatal acetaminophen exposure, residual confounding by social class cannot be completely discarded." Alemany 2021 at 1001 (citation omitted). Such a statement in no way purports to suggest that Alemany 2021 even addressed, much less adjusted for, genetics by, for example, employing a sibling-control design or negative control in the form of partner acetaminophen use.

likely in the form of gene-environment interactions, can play a role in ***some*** ASD cases. Rather, the salient point is that plaintiffs have no evidence that ***acetaminophen*** has a role in any such gene-environment interactions. Indeed, not even plaintiffs claim that there is a known gene that interacts with acetaminophen to increase the risk of ASD (much less to cause it). (*See* Rep. of Wendy Chung ¶¶ 128-144 (Mot. Ex. 15).) Although plaintiffs highlight Dr. Cabrera's citation to a study by Carter & Blizzard in which the authors purportedly "found that the number of autism susceptibility genes targeted by APAP exceeded all other tested compounds besides valproic acid" (Cabrera Opp'n at 16 (citing Cabrera Rep. at 176-77)), Dr. Cabrera expressly testified that there are too many "gaps in the data" with respect to epigenetics—changes in gene expression—for that theory to support plaintiffs' theory of general causation. (Cabrera Dep. 325:17-326:1.) And because "[l]aw lags behind science; it does not lead it," *In re Mirena IUS Levonorgestrel-Related Prods. Liab. Litig.*, 341 F. Supp. 3d 213, 270-71 (S.D.N.Y. 2018) (citation omitted), *aff'd*, 982 F.3d 113 (2d Cir. 2020), plaintiffs' speculative gene-interaction theory cannot supply the needed support for Dr. Cabrera's pontifications about genetic confounding.

Liew 2016. Plaintiffs also fail to identify a meaningful attempt by their experts to respond to Liew 2016's explicit warning that "residual confounding by indication or genetic factors [are] alternate explanations" for the small association reported between acetaminophen and ASD.[18] Plaintiffs attempt to supply their own rationale, seeking to minimize this explicit warning as a mere "theoretical possibility" (Baccarelli Opp'n at 11, 37), but as the primary author of Liew 2016 made clear one year later, the potential for genetic confounding was a

[18] Liew, *Maternal Use of Acetaminophen During Pregnancy and Risk of Autism Spectrum Disorders in Childhood: A Danish National Birth Cohort Study*, 9 Autism Research 951, 956 (2016) (Mot. Ex. 99).

"major concern."[19] Although Liew 2016 found a weak association between acetaminophen and ASD (aHR=1.19, 95% CI 1.04-1.35), when broken down to subtypes, the association only remained for ASD with HKD (aHR=1.51, 95% CI 1.19-1.92), and not for other subtypes of ASD. Moreover, these findings are at odds with plaintiffs' experts' other key study (Ji 2020), which reported no statistically significant increase in the risk of ASD with ADHD, but did report a statistically significant association between acetaminophen exposure and ASD without ADHD. These diametrically opposed findings defy comprehension because, as Dr. Hollander recognizes, "[b]oth ADHD and HKD refer to a combination of inattention, hyperactive, and impulsive behavior in children" (Am. Rep. of Eric Hollander at 41 (Mot. Ex. 11)), underscoring why it was particularly critical for plaintiffs' experts to meaningfully account for potential confounding. Plaintiffs are unable to show that Drs. Baccarelli or Cabrera did so, relying on the same ADHD- and non-diagnostic "studies in the literature" just discussed in connection with Ji 2020.

Plaintiffs barely address confounding by indication in their Cabrera opposition (Cabrera Opp'n at 20) and while they contend in their Baccarelli opposition that this concern "has been studied extensively and rejected by the authors publishing in this literature," as well as Dr. Pinto-Martin (Baccarelli Opp'n at 15), none of this is true. The only ASD-related study plaintiffs cite (Alemany 2021) expressly cautioned that "confounding by indication cannot be completely ruled out,"[20] and what Dr. Pinto-Martin actually said was that "the evidence on fever is compelling and interesting, and we don't understand the causal pathway." (Pinto-Martin Dep. 127:1-3.) That conclusion is echoed by the FDA, which likewise has concluded that the data cited by plaintiffs'

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[19] Olsen & Liew, *Commentary: Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function and Autism Spectrum Symptoms*, 45(6) Int'l J. Epidemiol. 1996, 1997 (2016) (Mot. Ex. 114).

[20] Alemany 2021 at 1000.

experts are "limited" by "their lack of adjustment for key confounders, namely indications like fever and headache/migraine."[21] Accordingly, as in *Daniels-Feasel*, plaintiffs' experts have misinterpreted, misapplied and disregarded fundamental limitations expressly acknowledged by the relevant studies' authors.

2. Drs. Baccarelli, Cabrera, Hollander And Louie Fail To Account For The Majority Of Scientific Evidence Reporting No Association.

As explained in defendants' opening brief, plaintiffs not only ignored or dismissed critical limitations in the epidemiologic literature, but also failed to meaningfully account for the two ASD-endpoint studies finding no statistically significant association (Ji 2018 and Saunders 2019) and a third reporting a similar finding in febrile women (Hornig 2018)—yet another telltale sign of an unreliable methodology. (*See* Mot. at 33-38.) Plaintiffs do not address Dr. Hollander's failure to address this critical evidence, much less attempt to defend it, and while they argue that Dr. Louie was not required to consider these unfavorable data because he is only "opining on . . . dose-response" (Louie Opp'n at 1), Dr. Louie's report contains a 15-page section purporting to analyze the "lines of evidence that support the causal association" (e.g., Ji 2020), not just those that supposedly evaluate dose-response. (Louie Rep. at 22-37 (capitalization altered).) Because Dr. Louie claims to have evaluated the body of epidemiologic literature, he was required to carefully "evaluate 'all of the scientific evidence,'" not just "cherry-pick from the 'scientific landscape.'" *Daniels-Feasel*, 2021 WL 4037820, at *5 (citations omitted).

Plaintiffs also argue that Drs. Baccarelli and Cabrera reported these conflicting studies, but their opposition briefs confirm that neither expert "analyze[d] the strengths and weaknesses of th[at] epidemiological research and explain[ed] why that body of research does not contradict

[21] FDA 2023 Review, at 3; *see also id.* at 17.

or undermine their opinion[s]." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 475 (E.D. Pa. 2014). Reconciling the majority of studies finding no statistically significant association "requires more than simply stating that the studies are wrong." *Norris v. Baxter Healthcare Corp*., 397 F.3d 878, 885-86 (10th Cir. 2005) (affirming exclusion of general causation evidence where experts "ignored or discounted without explanation the contrary epidemiological studies"; "[m]ere criticism of epidemiology cannot establish causation").

Ji 2018. Plaintiffs claim that Drs. Baccarelli and Cabrera considered this study and that it supports their opinions because it "showed an association, just not a significant one." (Baccarelli Opp'n at 39; *see also* Cabrera Opp'n at 19.) This argument is disingenuous. If Dr. Baccarelli believed that the statistically insignificant finding in Ji 2018 supported his opinion with respect to ASD, he would have said so in his initial report. Instead, he wrote that "[r]esults from this dataset" (Ji 2020) "were also reported earlier in a lower tier journal" and that he "utilized the most recent of the two papers in [his] review." (Baccarelli Rep. at 102.)[22] It was not until Dr. Pinto-Martin pointed this out in her own report that Dr. Baccarelli embraced the paper and twisted the results to support his opinion. *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 793-94, 799 (3d Cir. 2017) (affirming exclusion of expert who "classified insignificant odds ratios above one as supporting a 'consistent' causality result, downplaying the possibility that they support no association"). Plaintiffs also highlight that Ji 2018 "measured APAP levels in the mother's blood one to three days after she delivered the child, providing a

[22] Plaintiffs assert that Dr. Cabrera "extensively analyzed Ji (2018), including its limitations, *and* that it showed an association" (Cabrera Opp'n at 19), but the cite they provide corresponds to a nearly page-long discussion of the study's ***ADHD*** findings. (*See* Cabrera Rep. at 139.) The only aspect of that discussion that touches on the study's results for the ASD question is a single sentence stating that "there were no significant associations found between maternal plasma levels of acetaminophen metabolites and the risks of ASD diagnosis and other [development disorder] diagnoses." (*Id.*) Dr. Cabrera does not elaborate on that statement, much less explain how it does or does not support his opinion that acetaminophen causes ASD.

highly imperfect proxy for in utero APAP exposure." (Baccarelli Opp'n at 39 (citing Baccarelli Rebuttal Rep. at 12); *see also* Cabrera Opp'n at 20 n.14 (similar).) But Ji 2020—which is the cornerstone of these experts' opinions—is a similarly imperfect metric for in utero exposure because, as previously discussed, it "may at most reflect maternal use of acetaminophen during the peripartum period,"[23] which is not the "critical window of exposure," according to Dr. Cabrera. (Cabrera Dep. 23:13-24:2, 230:9-12.) In short, plaintiffs' and their experts' heads-I-win-tails-you-lose approach to Ji 2018 underscores the lengths to which they are willing to go to press their theory that acetaminophen causes ASD.

Saunders 2019. Plaintiffs argue that it was "reasonable" for Drs. Baccarelli and Cabrera to regard this retrospective case-control study as "inferior" to the ones they relied on because it "failed to control for virtually any confounders" and had a "far smaller sample size" than the other studies. (Baccarelli Opp'n at 39-40; *see also* Cabrera Opp'n at 20.) But as discussed in defendants' opening brief, the failure to control for confounding and retrospective case-control design (e.g., concerns over recall bias) would tend to artificially ***elevate*** any reported association, not ***diminish*** it. (Mot. at 36.) Plaintiffs do not respond to either argument—i.e., that those who suffer an adverse outcome are more likely to assert recollection of using a medication under study, and that controlling for confounding factors has reduced observed associations between environmental exposures and the development of ASD.[24] Nor do they address the fact that limitations regarding confounding are also a "concern . . . noted by studies [Drs. Baccarelli and Cabrera] cite[] for the existence of a statistically significant association." *Daniels-Feasel*, 2021

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[23] Ji 2020 at 188.

[24] *See, e.g.*, Baker, *Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity*, 174(11) JAMA Pediatrics 1073 (2020) ("Baker 2020") (Mot. Ex. 35); Leppert 2019 at 835.

WL 4037820, at *9 (failure to take limitations seriously when they undercut expert's opinions "casts significant doubt on the[ir] reliability").

Hornig 2018. Plaintiffs argue that Dr. Cabrera did not discuss Hornig 2018 in his report because "that study addressed prenatal fever, not APAP and ASD or ADHD." (Cabrera Opp'n at 20.) Plaintiffs similarly argue that Dr. Baccarelli gave it virtually no weight because "[t]hat is a study on the association between fever and ASD," which "says *nothing* about whether APAP is an independent risk factor." (Baccarelli Opp'n at 40.) Plaintiffs also speculate that "[i]t is entirely plausible that APAP itself increases the ASD risk and that reduction of fever decreases the ASD risk," but they cite nothing to support that hypothesis, and other studies have similarly showed that acetaminophen attenuated the association between fever and ASD symptoms.[25]

For these reasons, too, plaintiffs' experts' "selective and biased reliance" on limited epidemiologic data reflects "an unreliable application of purportedly sound scientific methodology." *Daniels-Feasel*, 2021 WL 4037820, at *12.

C. Drs. Baccarelli, Cabrera, Hollander And Louie's Reliance On Studies That Do Not Use Clinical ASD Diagnoses As Endpoints Is Also Unreliable.

Plaintiffs also fail to justify their experts' reliance on studies and meta-analyses that assessed a potential association between prenatal exposure to acetaminophen and various screening tools that measure non-specific neurodevelopmental symptoms.

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[25] *See* Liew, *Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study*, 27(6) Epidemiology 912, 915 (2016) (Mot. Ex. 101) ("Taking acetaminophen in pregnancy appeared to benefit children whose mothers reported fever in pregnancy, possibly due to acetaminophen treatment countering the negative impact of fever on child IQ scores."); *see also* Zerbo, *Is Maternal Influenza or Fever During Pregnancy Associated with Autism or Development Delays? Results from the CHARGE Study*, 43 J. Autism Dev. Disord. 25, 30 (2013) (Mot. Ex. 167) (OR for ASD attenuated when taking acetaminophen); FDA 2023 Review, at 15, 17 (noting that "fever and headache/migraine" share "collinearity with APAP use during pregnancy").

1. Proxy Studies That Do Not Involve Clinical Diagnoses Of ASD Do Not Provide A Reliable Basis For General Causation Opinions.

Plaintiffs' attempts to justify their experts' reliance on so-called "proxy" studies using various screening tools and questionnaires also fail.

First, plaintiffs contend that the non-specificity of "proxy" studies merely "goes to the *weight* to give non-endpoint studies." (Baccarelli Opp'n at 41; *see also* Hollander Opp'n at 16.) But many of the outcomes measured by these studies (e.g., child IQ or somatic complaints) are utterly irrelevant to an ASD diagnosis. (*See* Dep. of Eric Hollander ("Hollander Dep.") 351:5-14 (Mot. Ex. 13) (IQ is not a symptom of ASD or ADHD).) And even as to symptoms that can be a first step in an ASD diagnosis, plaintiffs concede that the "screening assessments may be overinclusive." (Hollander Opp'n at 19-20.) This is not merely an issue of weight. *See Hendrix v. Evenflo Co.*, 255 F.R.D. 568, 601-02 (N.D. Fla. 2009) (expert's reliance on a study using "simple autism screening tests" was the product of "faulty logic" (i.e., not a matter of weight)), *aff'd*, 609 F.3d 1183 (11th Cir. 2010).

Plaintiffs also list supposed "validation" studies that address the utility of various screening tests, but most address ADHD, not ASD (e.g., Algorta, Riglin, Overgaard, Oerbeck, Spencer).[26] And to the extent the studies address screening for ASD-related symptoms, they reinforce defendants' argument that screening tests are not a reliable metric for assessing causation. For example, Russell 2013 evaluated the predictive value of the Strength &

[26] Algorta, *Diagnostic Efficiency of the SDQ for Parents to Identify ADHD in the UK: A ROC Analysis*, 25 Euro. Child Adolesc. Psychiatry 949 (2016); Riglin, *Investigating the Validity of the Strengths and Difficulties Questionnaire to Assess ADHD in Young Adulthood*, 301 Psychiatry Research 1 (2021); Overgaard, *The Predictive Validity of the Strengths and Difficulties Questionnaire for Child Attention-Deficit/Hyperactivity Disorder*, 28 Euro. Child Adolesc. Psychiatry 625 (2019); Oerbeck, *Early Predictors of ADHD: Evidence from a Prospective Birth Cohort*, 24(12) J. Atten. Disord. 1685 (2020); Spencer, *Screening for Attention-Deficit/Hyperactivity Disorder and Comorbidities in a Diverse, Urban Primary Care Setting*, 57(12) Clin. Pediatrics 1442 (2018). Copies of all studies cited herein and not previously provided are attached to the Declaration of Kristen L. Richer as Exs. 2-14.

Difficulties Questionnaire ("SDQ") and concluded that "we do not currently recommend using the SDQ as a screening tool for either [ASD or ADHD] in clinical practice due to the high number of false positives and limitations of case definition in our study."[27] Similarly, Rescorla 2020 stated that the Child Behavior Checklist ("CBCL") "yields many false positives when used to differentiate children with ASD from those with other psychiatric and developmental problems."[28] For these reasons, it is widely recognized that screening tools are, at most, "mechanism[s] to identify young children at risk for ASD and other problems who can be referred for more detailed assessment";[29] they are not a substitute for "clinician judgment."[30]

Plaintiffs also contend that both the FDA and JJCI have endorsed the use of screening tools as part of a general causation inquiry (*see, e.g.*, Baccarelli Opp'n at 41; Hollander Opp'n at 13), but that claim is false. The FDA review cited by plaintiffs in their Baccarelli opposition "emphasiz[es] the subjective nature of non-diagnostic outcome assessments," noting that they "do not necessarily indicate a diagnosis of a specific disorder." ECF 483-1 at FDACDER000106 (cited in Baccarelli Opp'n at 41). That is why the FDA has recognized that studies attempting to measure proposed associations between environmental exposures and the development of ASD should "[a]ssess[] outcomes using a clinical diagnosis."[31] And the fact that JJCI evaluated studies involving screening tests speaks to its pharmacovigilance, not any supposed concession that they can support a theory of general causation. *See In re Mirena*, 202 F. Supp. 3d at 324-25

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[27] Russell, *The Strengths and Difficulties Questionnaire as a Predictor of Parent-Reported Diagnosis of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder*, 8(12) PloS One 1, 7 (2013) (Mot. Ex. 124).

[28] Rescorla, *The CBCL/1½–5's DSM-ASD Scale: Confirmatory Factor Analyses Across 24 Societies*, 50(9) J. Autism Dev. Disord. 3326, 3327 (2020).

[29] Levy, *ASD Screening with the Child Behavior Checklist/1.5-5 in the Study to Explore Early Development*, 49(6) J. Autism Dev. Disord. 2348, 2355 (2019).

[30] Mazefsky, *Child Behavior Checklist Scores for School-Aged Children with Autism: Preliminary Evidence of Patterns Suggesting the Need for Referral*, 33 J. Psychopathol. Behav. Assess. 31, 36 (2011).

[31] FDA 2023 Review, at 27.

(the fact that pharmaceutical company's employees "discuss[ed] the potential need for further investigation" "cannot serve as admissions of general causation"). Accordingly, the studies addressing screening tests do not provide "reliable support for the theory that" in utero exposure to acetaminophen "can lead to autism." *Hendrix*, 255 F.R.D. at 602.

Second, even if the screening tests were informative of a possible association, plaintiffs fail to refute defendants' argument that Drs. Baccarelli, Cabrera, Hollander and Louie cherry-pick favorable findings from those studies, while downplaying findings within the same papers that undercut their opinions. (*See* Mot. at 41-43.) Plaintiffs do not even respond to this argument in their Cabrera, Hollander and Louie oppositions, ignoring, for example, Dr. Cabrera's touting of Avella-Garcia 2016's finding of an association with ASD symptoms in male children (*see* Cabrera Rep. at 128-29), while simultaneously ignoring the same study's finding that female children with prenatal acetaminophen exposure had significantly lower CAST scores.[32] Plaintiffs similarly ignore Dr. Hollander's disregard of Tovo-Rodrigues 2020's conclusion that the authors could not "confirm the existence of an association between acetaminophen used during pregnancy and low neurodevelopmental performance,"[33] even though Dr. Hollander considers the CBCL to be "a good Level 1 screener of ASD." (Hollander Rebuttal Rep. at 24-25.)

Although plaintiffs do address these issues in their Baccarelli opposition, their arguments are unavailing. With respect to Avella-Garcia 2016, for example, plaintiffs claim that "Dr.

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[32] *See* Avella-Garcia, *Acetaminophen Use in Pregnancy and Neurodevelopment: Attention Function and Autism Spectrum Symptoms*, 45(6) Int'l J. Epidemiol. 1987, 1991 (2016) ("Avella-Garcia 2016") (Mot. Ex. 33).

[33] Tovo-Rodrigues, *Low Neurodevelopment Performance and Behavioural/Emotional Problems at 24 and 48 Months in Brazilian Children Exposed to Acetaminophen During Foetal Development*, 34 Paediatr. Perinat. Epidemiol. 278, 278 (2020) (Mot. Ex. 150).

Baccarelli specifically addresses *both* of th[e] findings," i.e., both the male and female groups. (Baccarelli Opp'n at 43 (citing Baccarelli Rep. at 98).) But Dr. Baccarelli described the study as "internal[ly] consisten[t]," an assertion that is indisputably untrue. (*See* Baccarelli Rep. at 20-21; *id.* at App. 1, at 4.) Plaintiffs also assert that Dr. Baccarelli was justified in downplaying the results from Leppert 2019 showing no association between acetaminophen and ASD symptoms on the ground that the authors of that study "never mention them." (Baccarelli Opp'n at 43.) But as plaintiffs acknowledge, those results were included in a supplementary table; the only reason they were not included in the body of the paper itself is because the study was primarily "designed to assess the correlation between genetics and pregnancy behavior." (*Id.*) By contrast, Dr. Baccarelli was retained to opine on the purported association between acetaminophen and ASD, requiring him to "consider[] all available evidence carefully," as opposed to dismissing null findings without any scientific explanation. *See Daniels-Feasel*, 2021 WL 4037820, at *5 (citation omitted).

2. Drs. Baccarelli, Cabrera, Hollander And Louie's Reliance On Two Meta-Analyses Is Also Unreliable.

Plaintiffs argue that Drs. Baccarelli, Cabrera, Hollander and Louie reliably considered two meta-analyses (Masarwa 2018 and Alemany 2021) because such studies "provide *more powerful* evidence regarding an association, not less." (Baccarelli Opp'n at 44; *see also* Cabrera Opp'n at 27.)[34] In so arguing, plaintiffs ignore defendants' argument that these meta-analyses are not informative because, as explained by Ricci 2023, there is "an insufficient number of comparable studies"[35]—i.e., only five epidemiological studies have actually assessed the

[34] Plaintiffs do not specifically address either Dr. Hollander's or Dr. Louie's reliance on these meta-analyses, apparently conceding defendants' arguments as to those experts.

[35] Ricci 2023 at 482.

proposed relationship between maternal use of acetaminophen and ASD diagnosis (one in the context of febrile women only), with the remainder of the studies focusing on the disparate and non-specific results of screening tools. Plaintiffs' silence on this issue is revealing given that they repeatedly tout Ricci 2023 as "evidence" that in utero exposure to acetaminophen causes ADHD. (*See, e.g.*, Baccarelli Opp'n at 5, 8, 15, 54.) Accordingly, plaintiffs' treatment of Ricci 2023—the most recent attempt at a meta-analysis of the very limited ASD-endpoint epidemiologic literature—follows the same "selective and biased" approach taken by their experts. *Daniels-Feasel*, 2021 WL 4037820, at *12.

3. Drs. Hollander, Baccarelli And Cabrera's "Transdiagnostic Approach" To NDDs Is Also Unreliable.

Plaintiffs' attempt to defend their experts' use of a so-called "transdiagnostic approach" to causation on the ground that "ASD and ADHD are not two distinct diseases, each with a separate and uniform presentation" (Hollander Opp'n at 6) is unscientific. "ASD symptoms are deficits in social communication and interaction, and restricted or repetitive patterns of behavior, interests, or activities." (*Id.*) By contrast, "ADHD symptoms are attention deficits and hyperactivity." (*Id.*) For this reason, ASD and ADHD have distinct sets of diagnostic criteria, with clear differences in developmental course, outcomes, and treatment plans.[36]

The materials highlighted in plaintiffs' Hollander opposition confirm that ASD and ADHD are distinct disorders. For example, plaintiffs point to a paper authored by defense expert

[36] *See* American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5). According to the DSM-5, typical manifestations of ASD include, *inter alia*, "failure to initiate or respond to social interactions," "abnormalities in eye contact and body language," "total lack of facial expressions and nonverbal communication," "difficulties in sharing imaginative play," "idiosyncratic phrases," and "excessive smelling or touching or objects." *Id.* at 50. By contrast, the DSM-5 list of behaviors emblematic of ADHD focuses on distinct and even some opposite behaviors like "talk[ing] excessively," "blurt[ing] out an answer before a question has been completed," or "fail[ing] to give close attention to details." *Id.* at 59-60.

Dr. Stephen Faraone, in which he states that "while there are some behavioral similarities between the two disorders, there are also both qualitative and quantitative differences in the behavioral phenotype."[37] Plaintiffs also note that the DSM-5 published in 2013 "combined ASD, ADHD, and other [NDDs] in a new chapter titled 'Neurodevelopmental Disorders.'" (Hollander Opp'n at 7 (citing Dep. of Stephen Faraone ("Faraone Dep.") 60:4-19 (Opp'n Ex. 31)).) However, as Dr. Faraone explained, the fact that multiple conditions were discussed in one chapter merely reflects "that their pathogenesis occurs during the development of the brain"—not that they are one and the same. (Faraone Dep. 60:9-22.)

In any event, overlapping symptomatology says nothing about the cause of either disorder and in no way provides a reliable basis for deeming their etiologies identical. *See Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002) (cited in Mot. at 45) (reliance on evidence that bromocriptine causes ischemic strokes was not a reliable basis for claiming that it also causes hemorrhagic strokes). Plaintiffs argue that, unlike in defendants' cases, Dr. Hollander's opinions are based "on the undisputed fact that they are disorders that *share* gene by environment origins and symptomologies." (Hollander Opp'n at 19.) But the materials plaintiffs highlight make clear that "there is . . . a ***unique*** genetic risk for" each of these disorders,[38] and to the extent they share some "genetic and environmental influences," those influences are also shared with "many other psychiatric disorders," including schizophrenia, depression, bipolar

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[37] Antschel, *The Comorbidity of ADHD & Autism Spectrum Disorder*, 13(10) Expert Rev. Neurother. 1117, 1118-20 (2013) ("Antschel 2013") (Opp'n Ex. 94). Notably, Antschel 2013 is not relied upon by Dr. Hollander and therefore cannot support the admissibility of his opinions. *See In re Rezulin*, 369 F. Supp. 2d at 407 ("The subject of this motion is the proposed testimony of experts, not the theories of the lawyers.").

[38] Faraone, *The World Federation of ADHD International Consensus Statement: 208 Evidence-Based Conclusions About the Disorder*, 128 Neurosci. Biobehav. Rev. 789, 795 (2021) (Mot. Ex. 71 & Opp'n Ex. 93) (emphasis added).

disorder, conduct disorder, eating disorders and substance use disorders.[39] Plaintiffs' experts have no evidence of any known gene that interacts with acetaminophen to increase the risk of any of these myriad NDDs (much less cause any of them); hence, extrapolating literature on the etiology of ADHD for purposes of opining on the cause of ASD is a "'leap of faith' supported by little more than the fact that both conditions" are NDDs. *Rider*, 295 F.3d at 1202.

Plaintiffs also argue that the "federal government . . . endorses Dr. Hollander's methodology" because the National Institute of Mental Health's Research Domain Criteria ("RDoC") Initiative "follows a similar path of reducing emphasis on diagnostic categories." (Hollander Opp'n at 8.) That is a gross distortion of the RDoC, which is "***not*** meant to serve as a diagnostic guide, nor is it intended to replace current diagnostic systems."[40] Rather, "[t]he aim is to understand the nature of mental health and illness in terms of varying degrees of dysfunction in fundamental psychological/biological systems."[41] The same document makes clear that the traditional (i.e., diagnostic) approach to "mental disorders—and the resulting diagnostic systems—provides benefits such as reliability and ease of diagnosis across a variety of contexts."[42] Accordingly, the federal government does not "endorse" Dr. Hollander's imprecise and over-inclusive approach to diagnosis, let alone use it to evaluate proposed associations and causal relationships.

Finally, plaintiffs argue that Dr. Hollander's "extensive experience diagnosing and

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39 *Id.*; *see also* Mattheisen, *Identification of Shared & Differentiating Genetic Architecture for Autism Spectrum Disorder, Attention-Deficit Hyperactivity Disorder & Case Subgroups*, 54(10) Nat. Genet. 1470, 1477 (2022) ("Mattheisen 2022") ("In conclusion, we have disentangled the shared and differentiating genetic liability underlying ASD and ADHD, identifying shared and disorder-specific risk variants providing information on pathophysiology."); Opp'n Ex. 102 (Mattheisen 2022 (abstract)).

40 Opp'n Ex. 113, at 1 (emphasis added).

41 *Id.*

42 *Id.* at 3.

treating" NDDs also supports the reliability of his opinions. (Hollander Opp'n at 18 (citation omitted).) But "[a]n anecdotal account of one expert's experience, however extensive or impressive the numbers it encompasses, does not by itself equate to a methodology, let alone one generally accepted by the relevant professional community." *Berk v. St. Vincent's Hosp. & Med. Ctr.*, 380 F. Supp. 2d 334, 354 (S.D.N.Y. 2005) (excluding causation opinion as not based on "good grounds") (citation omitted). *In re Mirena IUD Products Liability Litigation*, 169 F. Supp. 3d 396, 413 (S.D.N.Y. 2016) (cited in Hollander Opp'n at 18), does not hold otherwise. Although the court noted in the standard section of its *Daubert* ruling that "[i]n certain fields, experience is the predominant, if not sole, basis for a great deal of reliable expert testimony" (Hollander Opp'n at 18 (citation omitted)), it did not suggest that experience can support *ipse dixit* opinions. To the contrary, the court excluded an expert's general causation opinion that was purportedly based on "her experience and expertise" because of the "gap" between the "sources on which she purport[ed] to rely" and her ultimate conclusions. *In re Mirena*, 169 F. Supp. 3d at 451. That is the same infirmity that makes Dr. Hollander's opinions (and the related opinions of plaintiffs' other experts) inadmissible.

II. DRS. BACCARELLI, CABRERA AND HOLLANDER DID NOT CONDUCT RELIABLE BRADFORD HILL ANALYSES.

Plaintiffs concede that Dr. Hollander "appl[ied] a single Bradford Hill analysis to ASD and ADHD," recycling their argument that his transdiagnostic approach "supports" his opinions. (Hollander Opp'n at 20.) Although plaintiffs argue that Drs. Baccarelli and Cabrera "*separately* analyzed the literature concerning" ASD and ADHD (Cabrera Opp'n at 27; *see also* Baccarelli Opp'n at 27), they each conducted a single Bradford Hill analysis to assess whether in utero acetaminophen exposure causes NDDs (referencing "many of the [ASD and ADHD] studies" together in support of each of the Bradford Hill criteria). (*See, e.g.*, Baccarelli Rep. at 158-172;

see also Cabrera Rep. at 189-195 (addressing the causal relationship between acetaminophen "and neurodevelopmental toxicity" and repeatedly referencing the association "between fetal exposure to APAP and ASD/ADHD").) In any event, Drs. Baccarelli, Cabrera and Hollander disregarded fundamental scientific principles in rewriting or minimizing the Bradford Hill factors, which "suggests motivated, result-driven, reasoning." *See In re Mirena*, 341 F. Supp. 3d at 251.

A. The Conclusion By Drs. Baccarelli, Cabrera And Hollander That A Facially Weak Association Supports The Strength Requirement Is Patently Unreliable.

Plaintiffs argue that their experts reliably analyzed the strength factor because the "Ji and Baker studies showed risk ratios of above 2.0 and indeed 3.0"—which is "an order of magnitude stronger than the (causal) association of secondhand smoke and lung cancer." (Baccarelli Opp'n at 50; *see also* Cabrera Opp'n at 28 (incorporating Baccarelli Opp'n at 33-42); Hollander Opp'n at 21 (similar).) However, Baker 2020 is an ADHD study, and while Ji 2020 reported what Dr. Cabrera regarded as a "moderate" association for the third tertile of cord blood measurements (aOR=3.62, 95% CI 1.62-8.60) (Cabrera Rep. at 134, 175), Liew 2016 reported a crude hazard ratio of 1.22 and an adjusted hazard ratio of 1.19, while most of the studies using an ASD diagnosis as an endpoint have found no statistically significant association at all. Plaintiffs themselves do not appear to seriously believe that the strength-of-association factor can be satisfied in light of these data, which overall reflect fewer and weaker relative risks than those deemed insufficient to support causation in *Daniels-Feasel*. *See* 2021 WL 4037820, at *8-10 (risks of 3.34, 2.2 and 1.45). That is presumably why plaintiffs try to compensate for the weak literature on ASD by referencing the "statistically significant results" in the ADHD literature.

(Baccarelli Opp'n at 51.)[43] Even if that were proper, statistical significance is not the same as strength, which is an objective metric not satisfied by the literature.

B. Drs. Baccarelli, Cabrera And Hollander Use Unreliable Methodologies To Conclude That The Studies Are Consistent.

Plaintiffs argue that the consistency requirement is "obviously" satisfied because "[n]umerous study authors have said" so. (Baccarelli Opp'n at 52; *see also* Cabrera Opp'n at 28 (incorporating Baccarelli Opp'n at 48-58); Hollander Opp'n at 21 (same).) But the only study they cite making such a claim with respect to ASD is Alemany 2021—the findings of which were reduced to a non-significant level for both boys and girls when diagnostic data from Liew 2016 were used in place of Liew 2016's screening data. (*See* Hollander Dep. 292:25-293:25.) Moreover, Alemany 2021's Bradford Hill analysis—like that of plaintiffs' experts—does not account for the checkerboard of other ASD-endpoint data, including three studies that did not find a statistically significant association between acetaminophen and ASD, or the fundamental inconsistency between Liew 2016's reporting of a statistically significant association between acetaminophen and ASD with HKD and Ji 2020's reporting of no significant association between the medication and ASD comorbid with ADHD, a condition similar to ASD with HKD.

Plaintiffs also claim that their experts appropriately reasoned that the ASD-related findings are consistent if statistical significance is ignored because an epidemiology textbook states that a "set of results is [not] inconsistent simply because some results are 'statistically

[43] Plaintiffs concede that "[d]efendants are correct" that lower relative risks must be analyzed more carefully to account for potential confounding. (Baccarelli Opp'n at 52 n.59.) They nonetheless brush that fundamental epidemiologic principle aside on the ground that the so-called Bauer Consensus Statement noted that the results of one ***ADHD*** study were supposedly so "large" that "residual confounding . . . is a less likely explanation for [the] identified associations." (Baccarelli Opp'n at 52 n.59 (quoting Bauer, *Consensus Statement: Paracetamol Use During Pregnancy—A Call for Precautionary Action*, 17 Nature Revs. Endocrinology 757, 763 (2021) (emphasis added) (Mot. Ex. 39)).) That is both irrelevant to ASD and in any event, inaccurate, as set forth in defendants' concurrently filed ADHD Reply Brief.

significant' and some are not." (Baccarelli Opp'n at 53.)[44] But an expert cannot simply ignore the statistically insignificant nature of purportedly positive results in evaluating consistency, because doing so unscientifically "downplay[s] the possibility that [the insignificant positive results] support no association." *In re Zoloft*, 858 F.3d at 793-94, 799. Plaintiffs' experts did just that in attempting (unsuccessfully) to reconcile the inconsistent results of Ji 2020 and Liew 2016 with those of Ji 2018 and Saunders 2019; as they describe it, their experts rested on the supposed fact that the non-significant "odds ratio [of Ji 2018] was positive." (Baccarelli Opp'n at 39.) In any event, plaintiffs' experts not only ignored statistical significance, but also failed to account for the internally inconsistent findings of Liew 2016, the fact that those very findings cannot be squared with those of Ji 2020 (plaintiffs' experts' other key epidemiologic study), and the fact that multiple studies (Hornig 2018 and Leppert 2019) produced point estimates below 1.0, suggesting that acetaminophen has a ***protective*** effect. In short, despite Dr. Baccarelli's hyperbolic statements at his deposition, the literature on ASD is fundamentally inconsistent and there is no reliable way to conclude otherwise.

C. Drs. Baccarelli, Cabrera And Hollander Downplay The Specificity Requirement Without Any Scientific Basis.

Plaintiffs argue that their experts reliably evaluated the specificity factor because they concluded that this factor "is *not* satisfied—the answer [defendants] agree with." (Baccarelli Opp'n at 53.) But that misses the point, which is that Drs. Baccarelli, Cabrera and Hollander inappropriately deemed this Bradford Hill requirement dispensable, rather than conceding that it weighs against causation. (*See* Mot. at 54-56.)

D. Drs. Baccarelli, Cabrera And Hollander Did Not Reliably Identify A Dose-Response.

[44] Quoting Opp'n Ex. 63, at 66.

Plaintiffs' assertion that their experts' opinions on dose-response comport with the literature addressing ADHD or NDDs in general also highlights the unreliability of their ASD opinions. (Baker 2020, Liew 2014 and Ricci 2023). (Baccarelli Opp'n at 54; *see also* Cabrera Opp'n at 28; Hollander Opp'n at 21.) One of those studies—Ricci 2023—could not even complete a meta-analysis with respect to ASD due to the "insufficient number of comparable studies" and is thus devoid of any information regarding dose-response as to plaintiffs' experts' ASD theory of causation.[45] As for Alemany 2021, the authors expressly stated that "we did ***not*** address dose-response relationship" as part of Bradford Hill analysis because "dose and frequency of use were not harmonized across cohorts."[46] And although plaintiffs cite to a couple of ASD diagnosis studies relied upon by plaintiffs' experts that did attempt to assess dose-response (Liew 2016 and Ji 2020), the reported association in Liew 2016 ***declined*** from 2-5 weeks of use to 6-20 weeks of use, while Ji 2020, at most, measured acetaminophen exposure at or near birth.

E. Drs. Baccarelli, Cabrera And Hollander Do Not Offer Reliable Opinions About Biological Plausibility.

The gist of plaintiffs' argument regarding biological plausibility is that Drs. Baccarelli, Cabrera and Hollander "identified multiple 'reasonable or realistic,' 'possible' mechanisms by which prenatal APAP exposure can cause ASD and ADHD." (Baccarelli Opp'n at 55; *see, e.g.*, Cabrera Opp'n at 29-31; Hollander Opp'n at 21-22.) But even Dr. Ann Bauer aptly described the proposed biological theories as mere "hypotheses,"[47] which does not suffice to satisfy biological plausibility under *Daubert*. *See Onglyza Prod. Cases*, 307 Cal. Rptr. 3d 480, 490 (Ct. App.

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45 Ricci 2023 at 482.

46 Alemany 2021 at 1000-01 (emphasis added).

47 Bauer, *Prenatal Paracetamol Exposure and Child Neurodevelopment: A Review*, 101 Horm. Behav. 125, 135 (2018) (Mot. Ex. 40).

2023) ("a proposed hypothesis" does not satisfy the biological plausibility requirement). Although plaintiffs contend that the "Alemany authors identified many of the exact same mechanisms" in finding this Bradford Hill criterion satisfied (Baccarelli Opp'n at 55), the authors did not even mention plaintiffs' experts' primary theory—i.e., NAPQI (a metabolite of acetaminophen) formation and glutathione depletion—much less cite any original research assessing that theory.[48] (*See, e.g.*, Bio. Plaus. Br. at 3 (ECF 1165) (addressing Dr. Pearson's "primary" mechanistic theory); Bio. Plaus. Reply Br. at 9-16, incorporated herein.)

F. The Literature Is Incoherent.

Plaintiffs brush aside their experts' inability to "pinpoint precisely *when* and *how* APAP exposure causes neurodevelopmental harm" on the supposed ground that the coherence criterion "does not require scientific certainty as to the timing and mechanism of a relationship in order to determine whether it 'seriously conflicts' with known scientific facts." (Cabrera Opp'n at 31.) But the problem here is not a mere lack of certainty; the problem is that plaintiffs' experts cannot even provide a ballpark estimate of when the critical exposure window for developing ASD occurs. Such a gap in knowledge—particularly given that plaintiffs' experts' primary ASD-diagnosis study (Ji 2020) measured acetaminophen at or near birth—is a fundamental problem for plaintiffs because "[t]he courtroom is not the place for scientific guesswork." *In re Mirena*, 341 F. Supp. 3d at 270-71 (citation omitted).

Plaintiffs also attempt to defend Dr. Baccarelli's opinion that "causation from APAP" is "consistent with the rise in rates of NDDs seen over the past decades" (Baccarelli Opp'n at 55), despite Dr. Baccarelli's failure to account for the expansion of the ASD diagnostic criteria and increased efforts to diagnose children early in life. (Mot. at 60.) Although plaintiffs describe

[48] *See* Alemany 2021 at 1000.

these reasons for increases in ASD diagnoses as "wild conjecture" (Baccarelli Opp'n at 55), they are supported by widely accepted data and literature that Dr. Baccarelli does not address, once again demonstrating that he "selectively chose his support from the scientific landscape." *In re Rezulin*, 369 F. Supp. 2d at 425 (citation omitted) (expert must "acknowledge or account for that evidence" "tending to refute the expert's theory").

G. Drs. Baccarelli, Cabrera And Hollander's Opinions On Temporality Are Speculative.

Plaintiffs argue that their experts properly evaluated temporality by relying on studies "in which women were asked *at the time of pregnancy* whether they took APAP." (Baccarelli Opp'n at 56.) But the question here is whether the use of APAP preceded the most vulnerable period for fetal development. Since plaintiffs' experts do not even know when that is, they cannot reliably proclaim that temporality is satisfied.

H. Drs. Baccarelli, Cabrera And Hollander Offer Opinions On Analogy And Experiment That Are Illogical.

Plaintiffs argue that Drs. Baccarelli and Cabrera reliably analogize the proposed causal relationship between in utero exposure to acetaminophen and ASD to the supposed relationship between in utero exposure to valproic acid and ASD based on their reasoning that "valproic acid and APAP have similar effects on the developing fetus." (Baccarelli Opp'n at 57; *see also* Cabrera Opp'n at 32.) But plaintiffs' theories about the two medications' purportedly similar "effects" say nothing about whether the two drugs are chemically or otherwise similar. *See McClain*, 401 F.3d at 1246 (reversing admission of expert who "failed to show that the PPA analogy is valid or that the differences in chemical structure between PPA and ephedrine make no difference"). Although plaintiffs argue that their experts reliably apply this factor based on "animal studies, lab studies, ecological studies, and human pharmacokinetic studies" (Baccarelli Opp'n at 57; *see also* Cabrera Opp'n at 32), they are wrong for all the reasons set forth below

and in defendants' Biological Plausibility Brief (ECF 1165), and Biological Plausibility Reply.

III. ANIMAL STUDIES CANNOT FILL THE VOID IN THE EPIDEMIOLOGICAL LITERATURE.

Plaintiffs also fail to justify Drs. Cabrera and Pearson's reliance on various studies measuring the purported impact of acetaminophen on animal behavior, none of which can fill the void in the epidemiologic literature.

First, plaintiffs argue that animal studies are "routinely used in the scientific community." (Cabrera Opp'n at 22; *see also* Pearson Opp'n at 32.) As Judge Swain explained in *Daniels-Feasel*, however, "laboratory animal studies" can, at most, only generate hypotheses because "they require making the assumption that chemicals behave similarly in different species." *Daniels-Feasel*, 2021 WL 4037820, at *13 (citation omitted). Plaintiffs assert that the "court's concerns over animal data in that case stemmed from 'overwhelming contradictory epidemiological evidence.'" (Cabrera Opp'n at 24 (citation omitted).) But, as previously discussed, the epidemiologic data relied on by the plaintiffs' expert in *Daniels-Feasel* (i.e., three different studies reporting statistically significant associations) were, if anything, ***more*** robust than the limited data here. Nonetheless, the court found the use of animal data to be "particularly concerning" because, as the expert herself conceded, "animals cannot even be diagnosed with autism in the same way humans can" since "'human brains are different than rodent brains,' and animals 'are not communicative in the way . . . humans are.'" *Daniels-Feasel*, 2021 WL 4037820, at *16 (citation omitted). Plaintiffs do not dispute that Drs. Cabrera and Pearson have made the same concessions here. (*See, e.g.*, Cabrera Dep. 196:15-24, 191:15-21; *see also* Pearson Opp'n at 33 ("Of course, as Dr. Pearson readily admitted . . . rats and mice do not experience ASD and ADHD[.]").)

Plaintiffs nevertheless argue that their experts should be allowed to do exactly what

Daniels-Feasel rejected because [redacted] But pharmacovigilance is not an "admission[] of general causation." *In re Mirena*, 202 F. Supp. 3d at 324-25; *see also Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1367-69 (N.D. Ga. 2001) (animal studies conducted by the defendant did not constitute a reliable basis for a theory of general causation), *aff'd sub nom. Rider v. Sandoz Pharms. Corp.*, 295 F.3d 1194 (11th Cir. 2002). Nor can plaintiffs defend the reliability of their experts' use of animal studies on the ground that animal studies are cited in pregnancy warnings attached to other drugs that contain acetaminophen (Cabrera Opp'n at 23) because such labeling is "unreliable proof of medical causation." *In re Mirena*, 387 F. Supp. 3d at 355-56 (citation omitted).

Second, plaintiffs separately fail to refute defendants' argument that Drs. Cabrera and Pearson "cherry-pick [the] data" from animal studies, ignoring findings that undermine their conclusions. *Daniels-Feasel*, 2021 WL 4037820, at *16. With respect to Klein 2020, plaintiffs appear to concede that Dr. Pearson ignores that the rodents "did not present altered social behavior in the three-chamber test."[49] Although plaintiffs contend that Dr. Cabrera "report[ed]" that finding, they do not dispute that Dr. Cabrera never explained how such an inconsistent finding can be reconciled with his conclusion that the study nonetheless constitutes "clear evidence" that prenatal acetaminophen exposure impairs "learning or social behavior." (Cabrera Rep. at 126-27.) Plaintiffs attempt to defend Dr. Cabrera's reliance on Harshaw & Warner 2022 on the ground that it "found significant effects from APAP exposure on repetitive and social

[49] Klein, *Gestational Exposure to Paracetamol in Rats Induces Neurofunctional Alterations in the Progeny*, 77 Neurotoxicol. Teratol. 1, 5 (2020) (Mot. Ex. 94).

behavior." (Cabrera Opp'n at 26.) But nowhere does Dr. Cabrera even mention the authors' finding of no significant effect in marble burying behavior for mice exposed to acetaminophen,[50] a supposedly critical measure of ASD-like behavior, according to Dr. Pearson.[51] Plaintiffs also argue that Dr. Cabrera "explained why" Gould 2012—which found that acetaminophen enhanced social behavior in adult male mice—"support[s] the conclusion that APAP exposure causes behavioral alterations consistent with ASD." (Cabrera Opp'n at 25 (citing Cabrera Rep. at 83).) But the only expert who attempted to provide such an explanation is Dr. Pearson, who presses the *ipse dixit* opinion that any observed change from the baseline is relevant evidence of neurotoxicity. (*See* Pearson Opp'n at 23 (citing Rebuttal Rep. of Brandon Pearson at 4 (Mot. Ex. 18)).) This cannot be reconciled with Dr. Pearson's own list of direction-specific behavioral endpoints that he expects to be "associated with ASD" (e.g., "[f]ailing to spend more time in the chamber," which supposedly "indicates low interest in peers"). (Pearson Rep. at 40.) For all of these reasons, the animal data cannot fill the gaps in plaintiffs' experts' opinions.

IV. DRS. BACCARELLI AND LOUIE'S OPINIONS SHOULD BE EXCLUDED FOR ADDITIONAL REASONS.

A. Dr. Baccarelli's "Navigation Guide" Opinion Is Unreliable.

Dr. Baccarelli's reliance on the "Navigation Guide" employs a risk-utility, regulator-like approach to identifying potential risks, which cannot support a finding of causation. *See In re Mirena*, 387 F. Supp. 3d at 356. Plaintiffs contend that defendants' authorities are inapposite because they "address [the] FDA's standard of review for determining the safety of drugs." (Baccarelli Opp'n at 58.) But the "Navigation Guide" was devised to facilitate the EPA's

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[50] *See* Harshaw & Warner, *Interleukin-1β-Induced Inflammation and Acetaminophen During Infancy: Distinct and Interactive Effects on Social-Emotional and Repetitive Behavior in C57BL/6J Mice*, 220 Pharmacol. Biochem. Behav. 1, 5 (2022) (Mot. Ex. 77).

[51] *See* Am. Rep. of Brandon Pearson ("Pearson Rep.") at 42 (Mot. Ex. 8) ("The number of marbles buried are used to represent repetitive, compulsive-like behavior in rodents (ASD factor III).").

approach to "evaluating [environmental] risks" (Baccarelli Rep. at 12-23), rendering defendants' cases instructive. Although plaintiffs contend that the "Navigation Guide" "is routinely employed to evaluate causation" (Baccarelli Opp'n at 59), none of the articles cited by plaintiffs reached a full-blown causal conclusion like the one given by Dr. Baccarelli here.[52]

In any event, plaintiffs do not meaningfully defend Dr. Baccarelli's proffered application of the "Navigation Guide," devoting most of their argument to describing its components and asserting that "Dr. Baccarelli properly applied all four steps." (Baccarelli Opp'n at 58.) As previously discussed, "[p]laintiffs' mere assertion that their experts followed [such a] methodology[y] is insufficient to carry their burden that their experts' opinion is reliable." *In re Zantac*, 644 F. Supp. 3d at 1278 n.164. This is all the more true because Dr. Baccarelli's approach to the Navigation Guide is rife with fundamental methodological errors. Although plaintiffs note that the Navigation Guide "has been developed to reduce bias" (Baccarelli Opp'n at 57 (citation omitted)), one of the principal tools the creators of the methodology prescribed for accomplishing this goal is requiring multiple individuals to independently assess the available evidence—a critical step Dr. Baccarelli failed to follow. (*See* Dep. of Andrea Baccarelli 317:18-318:4 (Mot. Ex. 3); *id.* 333:20-335:5.) And it is presumably that failure that led Dr. Baccarelli to employ a facially biased application of the Navigation Guide steps by, for example, giving the Avella-Garcia 2016 study a "high level[] of consistency" even though the authors reported

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[52] *See* Marí-Bauset, *Endocrine Disruptors and Autism Spectrum Disorder in Pregnancy: A Review and Evaluation of the Quality of the Epidemiological Evidence*, 5(12) Children 1, 1 (2018) (cited in Baccarelli Opp'n at 59) (Opp'n Ex. 72) ("[O]ur objective was to summarize . . . the potential association between prenatal exposure to [endocrine disruptors chemicals] and Autism Spectrum Disorder . . . ."); Lam, *Developmental PBDE Exposure and IQ/ADHD in Childhood: a Systematic Review and Meta-Analysis*, 126(8) Environ. Health Perspect. 1, 2 (2017) (cited in Baccarelli Opp'n at 59) (Opp'n Ex. 73) (does "exposure to [polybrominated diphenyl ethers] in humans affect" "measures of intelligence" or "ADHD and attention-related behavioral" outcomes); Johnson, *Application of the Navigation Guide Systematic Review Methodology to the Evidence for Developmental and Reproductive Toxicity of Triclosan*, 92 Environ. Int'l 716, 716-17 (2016) (cited in Baccarelli Opp'n at 59) (Opp'n Ex. 74) ("Does exposure to triclosan have adverse effects on human development or reproduction?").

completely discordant findings on ASD symptoms between boys and girls and found no significant association between acetaminophen and ASD.[53]

B. Dr. Baccarelli's Litigation Opinions Are Separately Inadmissible Because They Contradict His Own Prior Published Opinions.

Plaintiffs do not seriously respond to defendants' argument that Dr. Baccarelli's opinions in this litigation cannot be squared with his prior published work, burying it in their voluminous background section, in which they assert that "in the years since the Laue study, the evidence has continued to pile up" (Baccarelli Opp'n at 5), and that Dr. Baccarelli was "blown away by the consistency" he allegedly found when examining the scientific landscape more recently. (*See id.* at 6 (citation omitted).) This argument lacks any credibility because, if anything, the studies published since 2019 undermine Dr. Baccarelli's newfound opinion that acetaminophen causes ADHD and ASD. Most notably, Gustavson 2021, the first and only ADHD study to rigorously employ a sibling-control design, found a near-complete attenuation of prior results. (*See* ADHD Br. at 25-26 (ECF 1162).) And the most recent publication on ASD, Ricci 2023, could not even reach a conclusion on ASD given the heterogeneity of results from prior publications. (*See* Mot. at 44.) Accordingly, plaintiffs' conclusory claims do not refute the only plausible explanation for Dr. Baccarelli's sudden epiphany: his opinions were manufactured for purposes of litigation.

C. Dr. Louie's Increased-Risk Opinions Are Unreliable.

Finally, plaintiffs fail to establish the reliability of Dr. Louie's increased-risk opinions—i.e., that prenatal exposure to acetaminophen for at least 28 cumulative days "increases the risk of ASD/ADHD development by two-fold as compared to [children] with no exposure to acetaminophen." (Louie Rep. ¶ 28.) The core of plaintiffs' argument is that Dr. Louie properly

[53] *See* Avella-Garcia 2016 at 1991.

relied on the studies addressed in defendants' opening brief. (*See* Louie Opp'n at 10.) But Liew 2016—the only study that looked at ASD diagnoses—"count[ed] total weeks of use," not days of use, and reported that an already weak 1.23 association at 2-5 weeks of use ***declined*** to 1.16 for 6-20 weeks of use. Liew 2014, Ystrom 2017 and Gustavson 2021 speak only to ADHD diagnoses (the latter of which performed a sibling-control analysis after which the prior reported association disappeared). Plaintiffs assert that Dr. Louie (like their other experts) "assigned virtually no weight" to Gustavson 2021 because it "was underpowered" (Louie Opp'n at 6), but that argument fails for all of the reasons set forth in defendants' ADHD briefing and opposition to plaintiffs' motion to exclude the opinions of Dr. Jennifer Pinto-Martin. (*See, e.g.*, ADHD Reply Br. at 9-10, incorporated herein; Pinto-Martin Opp'n at 22-25 (ECF 1241).)

The remaining studies address "behavioral" outcomes, none of which plaintiffs seriously defend in their Louie opposition, simply "incorporat[ing] by reference their oppositions to the motions to exclude Drs. Baccarelli and Hollander." (Louie Opp'n at 13.) As previously discussed, such "proxy" studies are not a reliable basis for opinions on general causation; it follows perforce that they are not a valid metric for opining on what level of exposure supposedly increases the risk of harm.[54] And even if they were, those studies broadly aggregate women who took acetaminophen anywhere from one to nine months of pregnancy, lumping women with widely varying exposures together in the 29+ days category. Plaintiffs respond "so what" (Louie Opp'n at 12), but the "what" is that Dr. Louie is essentially advancing the sweeping claim that in utero acetaminophen exposure for a cumulative period of 28 days or more increases the risk of two distinct NDDs in virtually the same way, regardless of when the exposure to the

[54] Plaintiffs appear to concede that Vlenterie 2016 cannot possibly support Dr. Louie's opinion because it "did not show a statistically significant association with [nine] behavioral outcomes." (Louie Opp'n at 6.) They also fail to explain how Gervin 2017—which assessed DNA methylation changes (a mechanistic theory that plaintiffs do not seriously attempt to defend)—is supportive of Dr. Louie's 28-days opinion. (*See* Bio. Plaus. Reply Br. at 15-16.)

medication occurs—or the amount of doses on those days—during the complex gestational process. The fact that none of the studies relied upon by Dr. Louie addresses—much less explains—when during the gestational period these exposures must have occurred is not only relevant, but it reinforces the incoherent, imprecise and highly speculative nature of plaintiffs' theories of general causation.[55]

CONCLUSION

For the foregoing reasons, as well as those set forth in defendants' opening brief, the Court should exclude the opinions of Drs. Baccarelli, Cabrera, Hollander, Louie and Pearson that maternal acetaminophen use during pregnancy can cause ASD in children.

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Respectfully submitted,

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[55] Plaintiffs all but abandon Dr. Louie's fallback opinion—i.e., that a cumulative dose over the course of pregnancy, ranging from 18,200 mg to 112,000 mg, increases the risk of developing ASD. As discussed in defendants' opening brief, none of the studies underlying this opinion (Ji 2020, Baker 2020, Anand 2021 and Alemany 2021) addresses dose at all. (*See* Mot. at 73-74.) Although plaintiffs now contend that these studies address "whether any elevation still occurs when controls are imposed for various biases and confounders" (Louie Opp'n at 6), that is just a repackaged epidemiologic opinion that fails for all of the reasons discussed herein and in defendants' ADHD Reply Brief.

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